

REMARKS/ARGUMENTS

The Status of the Claims.

Claims 34 to 55 and 63 to 69 are pending with entry of this amendment. Claims 1 to 33 and 56 to 62 were previously cancelled. Claims 34, 41, 42, 47, 49, 50, 54, 55 and 63 to 67 are amended herein. These amendments introduce no new matter and support is replete throughout the specification. These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record.

With respect to claim 34, the name of the RS of the construct has been amended to provide consistent usage in the claim, and throughout the claim set, as suggested in the Interview of October 22, 2009. Further, a typographical error in the name of the HTTP unnatural amino acid has been provided, as found throughout the original specification.

Claim 41 has been amended to remove a term objected to by the Office.

Claims 42, 49, 54, 55 and 63 to 67 are amended for consistent usage of the named O-RS.

Claim 50 is amended for consistent O-RS usage and to further clarify that the construct encodes the O-RS.

Applicants submit that no new matter has been added to the application by way of the above Amendment. Accordingly, entry of the Amendment is respectfully requested.

Interview Summary.

On October 22, 2009, Examiner Leavitt called Applicants' representative, Gary Baker, to discuss enablement of independent claims. In particular, the Examiner agreed that, e.g., a peptide at least 90% identical to SEQ ID NO: 2 with a Pro144 is the same regardless of the name given to the peptide. The Examiner requested the name used to identify synthetases be used consistently throughout the claim set to avoid confusion.

35 U.S.C. §112, Second Paragraph Indefiniteness.

Claim 41 was rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because it is allegedly unclear how to interpret what is considered "highly stringent conditions."

However, applicants note that highly stringent conditions are clearly and unambiguously described in the original specification, e.g., at paragraphs 99 and 100.

For example, in determining highly stringent hybridization and wash conditions, the hybridization and wash conditions are gradually increased (e.g., by increasing temperature, decreasing salt concentration, increasing detergent concentration and/or increasing the concentration of organic solvents such as formalin in the hybridization or wash), until a selected set of criteria are met. For example, the hybridization and wash conditions can be gradually increased until a probe binds to a perfectly matched complementary target with a signal to noise ratio that is at least 5x as high as that observed for hybridization of the probe to an unmatched target. For the purposes of the present invention, generally, "highly stringent" hybridization and wash conditions are selected to be about 5° C lower than the T_m for the specific sequence at a defined ionic strength and pH.

Because one of skill in the art routinely determines and practices highly stringent hybridization conditions, as described in the specification, the phrase can not be considered unclear. Applicants respectfully request withdrawal of the rejection.

Regarding indefiniteness rejections to claims 47 and 50, Applicants appreciate the careful reading of the Examiner. Applicants have made amendments addressing the issues raised and request withdrawal of the indefiniteness rejections of these claims.

35 U.S.C. §112, Second Paragraph New Matter.

Claim were was rejected under 35 U.S.C. §112, second paragraph, as allegedly failing the written description requirement based on the presence of new matter.

The rejection was based on the typographical error or "HTTP" in claim 34, as compared to the more proper "5-HTTP". Applicants appreciate the careful review given the claim by the Examiner and have amended the claim to correct the inadvertent mistake.

Applicants respectfully request withdrawal of the new matter rejection.

35 U.S.C. §112, First Paragraph.

Claims 34 to 55 and 63 to 67 were rejected under 35 U.S.C. §112, first paragraph, for alleged lack of adequate enablement. To the extent the rejection is deemed applicable to the currently amended claims, Applicants traverse.

In the present Action, the Office has acknowledged enablement for the following claim (adjusted from claim 34 of the May 22, 2009, RCE):

A method of incorporating a 5-substituted tryptophan unnatural amino acid into a peptide, the method comprising:

preparing a construct comprising a nucleic acid sequence encoding an orthogonal mutant tryptophanyl-tRNA synthetase (O-muTrpRS) and comprising at least 90% identity to the sequence of SEQ ID NO: 2, the O-muTrpRS comprising a proline residue at a position corresponding to position 144 of SEQ ID NO: 2, wherein the O-muTrpRS aminoacylates an orthogonal ~~a reference~~ tRNA (O-tRNA) of SEQ ID No: 3 with a 5-substituted tryptophan, 5-substituted tryptophan analog or 5-hydroxy-L-tryptophan (5-HHTTP) when the ~~reference~~ O-tRNA, 5-substituted tryptophan analog or 5-HHTTP, and the O-muTrpRS are present in a eukaryotic cell;

preparing a construct comprising a nucleic acid sequence encoding an orthogonal tRNA (O-tRNA) comprising: at least 90% identity to SEQ ID NO: 3, wherein the O-tRNA is aminoacylated with the 5-substituted tryptophan analog or 5-HHTTP by the ~~a reference~~ O-muTrpRS of SEQ ID NO: 2 when the O-muTrpRS, 5-substituted tryptophan analog or 5-HHTTP, and the O-tRNA are present in eukaryotic cell;

introducing the O-muTrpRS construct and the O-tRNA construct into the eukaryotic cell; and,

preferentially aminoacylating an expressed O-tRNA with the unnatural amino acid, wherein said aminoacylation is catalyzed by an expressed O-muTrpRS;

whereby the 5-substituted tryptophan unnatural amino acid or 5-HHTTP is incorporated into the peptide in the cell.

As a preliminary matter, in light of the Interview of October 22, 2009, and the acknowledged enabled claim above, the present claims should be considered enabled and

allowable. While the Office's suggested name for the RS of the enabled construct is uniformly "O-muTrpRS", Applicants have uniformly identified the RS of the construct as the "O-RS". As agreed in the interview, the name does not matter where the RS of the claims is limited to, e.g., comprising at least 90% identity to the sequence of SEQ ID NO: 2, the O-muTrpRS comprising a proline residue at a position corresponding to position 144 of SEQ ID NO: 2.

In a side issue, note that the currently amended claims include a requirement that, e.g., the O-RS be interactive with a clearly identified standard "reference" tRNA of SEQ ID No: 3; and, the O-tRNA be interactive with a clearly identified standard "reference" RS of SEQ ID No: 2. For example, orthogonal pair members of the methods in the cell can vary but must, e.g., retain interactivity with their original complimentary pair partner, as identified in the original specification. The Office has suggested in related cases that this enhances enablement by bringing more certainty and consistency to the aminoacylation activity parameter of the claims.

To be an enabling disclosure under § 112, first paragraph, a patent must contain a description that enables one skilled in the art to make and use the claimed invention. That some experimentation is necessary does not constitute a lack of enablement; the amount of experimentation, however, must not be unduly extensive. See *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Whether undue experimentation is required by one skilled in the art is typically determined by reference to eight factors considered relevant to the inquiry: (1) quantity of experimentation necessary; (2) amount of guidance presented; (3) presence of working examples; (4) nature of the invention; (5) state of the prior art; (6) relative skill of those in the art; (7) predictability of the art; and (8) breadth of the claims. See *id.*

The present methods are enabled because they employ functionally identified structures variable within a range routinely practiced by one of skill without undue experimentation. The claims are tailored for reasonable scope around working embodiments. Guidance is extensive, e.g., with full functioning working example structures identified at every position and identification of key structures associated with desired activities. The skill in the art is high and one of ordinary skill in the protein engineering arts can readily and

predictably practice methods across the range of the claims (e.g., see Guo - Protein Tolerance to Random Amino Acid Change, PNAS 101: 9205).

Because the amended claims have essentially the scope deemed enabled in the Action (but for an immaterial difference in the naming of the RS in the method), Applicants respectfully request withdrawal of the rejections for alleged lack of enablement.

Claim Objections.

Claims 41 and 42 were objected to for allegedly failing to further limit the parent claim 34. To the extent the rejection is deemed applicable to the amended claims, Applicants traverse.

Claim 41 was objected to as allegedly not further limiting parent claim 34 for "scope ...extend[ing] beyond that of claim 34." The objection variously alleges over broadening by conservative variations, high stringency hybridization and orthogonal pair interactions.

As a preliminary matter, Applicants note that the scope of claim 41 can not extend beyond the scope of claim 34, because dependent claims include all limitations of the parent claims.

The Office has objected to the term "conservative variants". Applicants note that the conservative variants of claim 41 would have to remain within the 90% identity and Pro144 limitations of the parent claim. Moreover, conservative variants are further limiting because such variations are of distinct types extensively discussed in the original specification (see, e.g., Table 1 and "Conservative Variations" section starting at paragraph 92). However, in the spirit of cooperation and to expedite the present prosecution, Applicants have deleted the objected term.

With regard to the "high stringency hybridization" aspect, again Applicants note that dependent claims can not be broader than a claim upon which they are dependent. Although the Office suggests that "any stretch of 100 or more consecutive homologous nucleotides can hybridize under high stringency", applicants note that the parent claim 34 does not require as much. For example, the sequences of parent claim 34 are not so limited. Moreover, the rejection fails to address the actual claim 41 language "hybridizes under highly stringent conditions over an entire length of" the sequence. Emphasis added. Because

the objected aspect does further limit the parent claim, Applicants respectfully request withdrawal of this objection.

With regard to orthogonal pair interactions, again Applicants note that dependent claims can not be broader than a claim upon which they are dependent. One does not have to reiterate the limitations of a parent claim in each dependent claim in order for the claim to be further limiting. Currently amended parent claim 34 includes aspects requiring functional interactions of components. Nothing in claim 41 allows, e.g., improper interactions between O-RSs and O-tRNAs that could possibly broaden the scope of claim 41 beyond that of parent claim 34. Indeed, the aspects a)-d) are each further limiting over the more generic parent claim 34.

Objected claim 42 further limits currently amended parent claim 34. For example, claim 34 does not require that the O-RS be essentially "derived from" or engineered based on a TrpRS structure, whereas claim 42 does. Applicants respectfully request withdrawal of the objection, e.g., in light of current amendments.

CONCLUSION

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, a telephone interview with the Examiner is hereby requested. Please telephone the undersigned at (510) 769-3510 to schedule an interview.

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Respectfully submitted,



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Appl. No. 10/580,987
Response Dated November 5, 2009
Reply to Office Action of July 24, 2009

Attachments:

- 1) A petition to extend the period of response for **1** month;
- 2) A transmittal sheet;
- 3) A fee transmittal sheet; and,
- 4) A receipt indication postcard.